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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/696,909	10/29/2003	James B. Lorens	7946-79836-01	9257
74839	7590	11/05/2010		
Klarquist Sparkman, LLP 121 SW Salmon St Suite 1600 Portland, OR 97204			EXAMINER REDDIG, PETER J	
			ART UNIT 1642	PAPER NUMBER
			NOTIFICATION DATE 11/05/2010	DELIVERY MODE ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

tanya.harding@klarquist.com  
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<b>Office Action Summary</b>	<b>Application No.</b> 10/696,909	<b>Applicant(s)</b> LORENS ET AL.	
	<b>Examiner</b> PETER J. REDDIG	<b>Art Unit</b> 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 17 August 2010.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1, 14-18, 27, 41-44, 54 and 55 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1, 14-18, 27, 41-44, 54 and 55 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                    | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)         | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____   | 6) <input type="checkbox"/> Other: _____                          |

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### **DETAILED ACTION**

1. The Amendment filed August 17, 2010 in response to the Office Action of May 27, 2010 is acknowledged and has been entered. Previously pending claims 2-13, 19-26, 28-40, 45-53, and 56-63 have been cancelled, claims 1 and 27 have been amended and new claims 55-61 have been added. Claims 1, 14-18, 27, 41-44, 54 and 55 are currently being examined.

### ***Rejections Maintained***

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

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invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

2. Claims 1, 14-18, 27, 41-44, 54 and 55 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Mor, O. (US Pat. App. Pub. 2003/0157573 A1 Feb. 12, 2002) as applied to claims, 1 14, 15, 16, 18, 27, 41, 42, 44, 54, 55, 56-58, 60, and 61 above, further in view of Klinghoffer et al. (United States Patent Application Publication No.: 2004/0077574, May 23, 2002, previously cited), further in view of O'Donnell et al. (Am. J. Path. 1999, 154: 1171-1180, IDS item), and, further in view of Varner and Cheresh (Current Opinion in Cell Biology, October 1996, 8:724-730, previously cited) for the reasons of record set forth below.

Mor teaches identifying an inhibitor Axl by determining the ability of compounds such as antibodies, antisense molecules, and small organic molecules to inhibit the Axl kinase activity in cells, like endothelial cells, expressing endogenous or human Axl, which comprises SEQ ID NO: 4, determining the inhibition of Axl kinase activity *in vitro*, and by determining cell survival, cell differentiation, or cell proliferation response to the compound. See claims 1-19, 21-23, and 35, Abstract, ¶ 0020, 0022, 0033-0036, 0045, 0046, 0049-0064, 0108, 0249, 0255, and Appendix 1 and 2. Mor teaches determining decreases in expression of the Axl polypeptide in response to the compounds. See ¶ 0065. Mor teaches that the identified drugs may be used as anti-angiogenic drugs for the treatment of cancer by preventing or reducing the proliferation of endothelial cells. See ¶ 0090.

Mor teaches as set forth above, and teaches that activation of Axl increases the survival of endothelial cells and induces migration of vascular muscle cells, but does not specifically teach using RNAi as a compound or assaying of  $\alpha V\beta 3$  expression, tube formation, or haptotaxis.

Klinghoffer et al. teach that siRNA/RNAi polynucleotides offer advantages over other types of polynucleotides for sequence specific alteration of gene expression including lower effective siRNA/RNAi polynucleotide concentration, enhance stability, shorter lengths, they are readily taken up by intact cells, and are effective at concentration that are several orders of magnitude lower than those required for either antisense or ribozyme polynucleotides, see paragraph 0022 and 0025.

O'Donnell et al. teach that Axl exhibits homophilic binding via its extracellular domain, which could be relevant to tube formation in angiogenesis. See p. 1176-2nd col. O'Donnell et al. teach that the ligand of Axl, Gas6, has multiple properties relevant to vascular biology including promoting adhesion of Axl expressing cells and stimulation of chemotaxis of vascular smooth muscle cells. See p. 1177-2nd col.

Varner and Cheresh teach that integrin of  $\alpha V\beta 3$  is significantly upregulated on vascular cells within human tumors and in response to growth factors and plays a biological role in a

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critical event of blood vessel formation during tumor angiogenesis by promoting vascular cell survival and that inhibition of  $\alpha V\beta 3$  inhibits angiogenesis, see section on Role of Integrins in Tumor Angiogenesis, p. 726- 727.

It would have been *prima facie* obvious at the time the invention was made to combine teachings of Mor and Klinghoffer et al. and use RNAi molecules in the screening methods of Mor because Klinghoffer et al. teach the advantages of siRNA as inhibitory molecules and one would have been motivated to identify the most effective inhibitory molecule in the screens of Mor to identify the most effective anti-angiogenic drug. Given that screening assays are routinely performed in the art, one of skill in the art would have a reasonable expectation of success of making and using the claimed assay.

Additionally, it would have been *prima facie* obvious at the time the invention was made to combine teachings of Mor, O'Donnell et al., and Varner and Cheresh and measure  $\alpha V\beta 3$  expression or tube formation in endothelial cells in response to the test compounds because Mor teaches assaying cellular differentiation in the screening assays for identifying angiogenesis inhibitors, O'Donnell et al. teaches that Axl may be involved in tube formation during and angiogenesis, and Varner and Cheresh teach that  $\alpha V\beta 3$  expression plays a critical event of blood vessel formation during tumor angiogenesis,  $\alpha V\beta 3$  is important for endothelial cell survival (like Axl), and inhibition of  $\alpha V\beta 3$  inhibits angiogenesis.

Applicants argue that as an initial matter, Applicants note that claim 17 depends from claim 1 and claim 43 depends from claim 27. Independent claims 1 and 27 have not been rejected under 35 U.S.C. § 103(a). If an independent claim is nonobvious, then any claim depending from the independent claim is nonobvious (MPEP § 2143.03, citing *In re Fine* 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)). Therefore, claims 17 and 43 cannot be obvious, unless claims 1 and 27 are rejected as obvious. In spite of this, and in light of the amendments to claims 1 and 27 above, the obviousness rejection as applied to canceled independent claims 62 and 63 is addressed below.

Applicants argue that the Office acknowledges that Mor does not disclose use of RNAi or assaying  $\alpha V\beta 3$  expression, tube formation, or haptotaxis (Office action, page 5, third paragraph). The Office asserts that it would have been obvious to combine Mor with Klinghoffer et al. to utilize RNAi molecules in the screening method of Mor (Office action, page 6, third paragraph).

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The Office also asserts that it would have been obvious to combine Mor, O'Donnell et al., and Varner and Cheresh because O'Donnell et al. discloses that Axl may be involved in tube formation during angiogenesis, and Varner and Cheresh disclose a role for  $\alpha V\beta 3$  in angiogenesis (Office action, page 6-7).

Applicants argue that Claims 1 and 27 are amended as discussed above to recite "an angiogenesis phenotype selected from  $\alpha V\beta 3$ , expression, tube formation, and haptotaxis..." The Office has provided no evidence that one of skill in the art would be motivated to combine Mor and Klinghoffer et al. to arrive at the claimed methods. Mor does not discuss angiogenesis phenotypes in general, nor  $\alpha V\beta 3$  expression, tube formation, or haptotaxis specifically. Mor is focused on identifying compounds of use in treating renal disease, specifically glomerulosclerosis and renal fibrosis in diabetic nephropathy (e.g., paragraphs [0020], [0022], and [0033]). Klinghoffer et al. relates solely to RNAi molecules, and does not cure the deficiencies of Mor.

Applicants argue that O'Donnell et al. state that Axl is expressed by endothelial cells in capillaries and the homophilic binding between extracellular domains "suggests a role in cell adhesion which could be relevant to tube formation in angiogenesis. Vascular smooth muscle cell expression has been previously noted in the rat and may suggest involvement of Axl in some other aspect of vascular function" (O'Donnell et al., page 1176, col. 2, emphasis added). However, the focus of O'Donnell et al. is on the effects of Gas6 on apoptosis or cell viability in cells which have been serum-deprived or exposed to  $TNF\alpha$  (O'Donnell et al., page 1172, first full paragraph and pages 1174-1176). Statements by O'Donnell et al. regarding the potential role of Axl in tube formation are speculative at best, and suggest equally that Axl may have some

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entirely different function in endothelial cells. The Office has not provided any evidence that one of skill in the art would have considered  $\alpha V\beta 3$  expression relevant or useful in the assays disclosed by Mor, nor would this have been predictable.

Applicants argue that based on the foregoing, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 103(a).

Applicants' arguments have been considered, but have not been found persuasive. First, with regard to the initial matter and the obviousness of the independent claims, all of the claims were recited in the USC 103 rejection and thus were rejected. With regard to the rejection, Mor specifically teaches that the drugs identified can be used as anti-angiogenic drugs, see ¶0090, and O'Donnell clearly shows that Axl is expressed in endothelial cells and is involved in their viability and survival, see Abstract. Additionally, Varner and Cheresch teach that integrin of  $\alpha V\beta 3$  is important in endothelial cell survival, see p. 726- 727. Thus, although the role of Axl in tube formation or  $\alpha V\beta 3$  expression may not be completely defined, given the art teaches that these are important aspects of angiogenesis by endothelial cells, it would have been obvious for one of skill in the art to assay these function in an effort to identify an angiogenesis inhibitor in addition to assaying a test compound's effect on Axl activity, given that they both have a role in endothelial cell function and angiogenesis.

Although Klinghoffer does not teach  $\alpha V\beta 3$  expression, tube formation, or haptotaxis, it was applied to show the obviousness of screening RNAi molecules for activity against angiogenesis. It must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references which made up the state of the art with regard to the claimed

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invention. Applicant's claimed invention fails to patentably distinguish over the state of the art represented by the cited references taken in combination. Thus, the rejection is maintained for the reasons previously set forth.

3. All other objections and rejections recited in the Office Action of 05/27/2010 are withdrawn.

4. No claims allowed.

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Misook Yu can be reached on (571) 272-0839. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.



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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Peter J Reddig/  
Primary Examiner, Art Unit 1642